Amendments to the Drawings:

Please replace Figures 8 and 9 in the specification with the attached replacement sheets. Figures 8 and 9 in the replacement sheets have improved photo quality.

Attachment: 2 replacement sheets

REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims. Claims 1-4 have been amended. Claim 5 has been cancelled without prejudice. After entry of the amendment, claims 1-4 and 6-25 will be pending. The Examiner has withdrawn claims 13-25 from consideration.

Applicants submit the amendments are supported by the specification and do not raise any issues of new matter.

Drawings

The Office Action alleges that Figures 8 and 9 are too dark. Replacement pages for Figures 8 and 9 are included herewith. Withdrawal of this objection is respectfully requested.

Enablement

Claims 1-12 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants respectfully traverse this rejection.

The Office Action acknowledges that the specification enables an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2. The Office Action, however, asserts the specification does not enable an isolated polypeptide comprising an amino acid sequence having at least about 80%, 85%, 90%, 95%, or 100% identity to amino acid residues X to 105 of SEQ ID NO:2 wherein X is an amino acid residue from 14 to 24 of SEQ ID NO:2 and the polypeptide promotes proliferation of ACE cells. Applicants respectfully do not agree.

In order to clarify the claimed invention, the claims have been amended to recite a single reference sequence. Amino acid residues 20 to 105 of SEQ ID NO:2 correspond to a mature form of EG-VEGF. See, for example, the specification at page 10, lines 20-21, page 79, lines 6-14 and Figure 16A.

The Office Action cites several references to support the rejection. Citing Ngo et al., Attwood et al., and Skolnick et al., the Office Action alleges the relationship between an amino acid sequence and its activity is unpredictable and that current sequence based methods for predicting structure and function are inadequate and unreliable. Brenner et al., however, discloses that % sequence identity comparison methods are adequate and useful for predicting shared function (Brenner et al., 1998, *Science*, 95:6073-6078 (copy enclosed)).

Brenner et al. extracted the sequences of domains of proteins in the Protein Data Bank creating a database of domains that were used to assess sequence comparison methods. Using this database, Brenner et al. found that pairwise sequence comparison methods are capable of detecting almost all relationships between proteins whose sequence identities are greater than 30% (Brenner et al., Abstract at page 6073 and figure 3 at page 6075). Pairwise sequence comparison methods that utilized statistical scores, such as E-values, recognized greater than 90% of the homologous pairs with 30-40% identity (Brenner et al. at page 6077) leading Brenner et al. to conclude that E-values give fairly accurate estimates of the significance of pairwise sequence matches and that the homologous proteins found by sequence comparison can be distinguished with high reliability from the huge number of unrelated pairs. (Brenner et al. at pages 6077-6078). The Brenner et al. study validated the use of sequence comparison methods to establish that % sequence identity comparisons greater than 30% are predictive of shared function.

Citing Mikayama et al., the Office Action alleges a single amino acid change can have dramatic effects on a protein's function. Bowie et al., however, disclose that proteins are surprisingly tolerant of amino acid substitutions (Bowie et al., 1990, *Science*, 247:1306-1310 (copy enclosed)). In addition, the Office Action has not provided any evidence that a single amino acid change to an angiogenic factor, such as EG-VEGF, would completely destroy its activity.

The specification contains sufficient disclosure to enable the scope of the claimed genus of EG-VEGF polypeptides. The specification describes techniques and guidelines for making EG-VEGF variants, including amino acid sequence comparison methods and exemplary and preferred amino acid substitutions (see specification at page 14, line 17 to page 16, line 15; page 30, line 22 to page 33, line 23; and Table 1 at page 32). Example 1 describes how to isolate cDNA clones encoding EG-VEGF, including the signal sequence finding algorithm used to identify cDNA clones. Example 2 describes how to use DNA comprising the coding sequence of mature EG-VEGF, for example, as a probe to screen for homologous DNAs encoding, for example, naturally occurring variants of EG-VEGF. Examples 3-6 describe how to express EG-VEGF in cells. Example 7 describes how to make antibodies that specifically bind EG-VEGF.

Example 8 describes how to purify EG-VEGF using anti-EG-VEGF antibodies. Example 14 describes how to screen EG-VEGF for ACE cell proliferation activity.

One of skill in the art would have been able to identify EG-VEGF variants without undue experimentation using the EST techniques, hybridization probes, or anti-EG-VEGF antibodies described in the specification. Applicants' post filing publication, in which mouse EG-VEGF was identified using an EST highly related to human EG-VEGF, confirms the teachings of the specification. See LeCouter et al., 2003, *Endocrinology*, 144:2606-2616 (copy enclosed). Mouse EG-VEGF has 88% identity to amino acid residues 20-105 of SEQ ID NO:2 and induces proliferation of ACE cells (see Figures 1B and 7A in LeCouter et al.).

Other post filing publications have identified EG-VEGF variants. Masuda et al. identified rat EG-VEGF, which has approximately 91% identity with amino acid residues 20-105 of SEQ ID NO:2 and induces mitogenesis of ACE cells (Masuda et al., 2002, *Biochem. Biophys. Res. Commun.*, 293:396-402 (copy enclosed)). Kisliouk et al. identified bovine EG-VEGF, which has approximately 88% identity with amino acid residues 20-105 of SEQ ID NO:2 and induces proliferation of endocrine gland-derived endothelial cells (Kisliouk et al., 2005, *Endocrinology*, 146:3950-3958 (copy enclosed)). See the amino acid sequence alignment of identified EG-VEGF species in Table 1.

Table 1

```
CLUSTAL W (1.8) multiple sequence alignment of EG-VEGF species

HuEG-VEGF       AVITGACERDVQCGAGTCCAISLWLRGLRMCTPLGREGEECHPGSHKVPFFRKRKHHTCP
RtEG-VEGF       AVITGACERDVQCGAGTCCAISLWLRGLRLCTPLGREGEECHPGSHKIPFFRKRQHHTCP
BvEG-VEGF       AVITGACERDVQCRAGTCCAVSLWLRGLRVCTPLGRAGEECHPGSHKVPFFRKRQHHACP
MsEG-VEGF       AVITGACERDIQCGAGTCCAISLWLRGLRLCTPLGREGEECHPGSHKIPFLRKRQHHTCP
                ********** :** ****** :******** :****** ********** :** :*** :** :**

HuEG-VEGF       CLPNLLCSRFPDGRYRCSMDLKNINF
RtEG-VEGF       CSPSLLCSRFPDGRYRCSQDLKNVNF
BvEG-VEGF       CLPNLLCSRGLDGRYRCSTNLKNINF
MuEG-VEGF       CSPSLLCSRFPDGRYRCFRDLKNANF
                * *.***** ****** :*** **
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	Species	% Identity to Mature Human EG-VEGF*	Reference
HuEG-VEGF	human	100	Specification at Figure 16A

RtEG-VEGF	rat	91	Masuda et al., 2002, *Biochem. Biopyhs. Res. Commun.*, 293:396-402.
BvEG-VEGF	bovine	88	Kisliouk et al., 2005, *Endocrinology*, 146:3950-3958.
MuEG-VEGF	mouse	88	LeCouter et al., 2003, *Endocrinology*, 144:2606-2616.

* Amino acid residues 20-105 of SEQ ID NO:2.

The Office Action alleges the specification lacks an *in vivo* working example demonstrating the EG-VEGF could treat any disease and that recent failures in clinical trails using VEGF antagonists indicate the unpredictability of angiogenesis inhibitors for treating disease, such as cancer. As a preliminary matter, Applicant's note the claims currently under examination are drawn to EG-VEGF polypeptides and not methods of treating a disease with an EG-VEGF antagonist. In contrast to the Examiner's opinions regarding VEGF antagonists, the VEGF antagonist bevaczimuab was recently approved by the FDA for the treatment of cancer (see enclosed press release).

The Office Action alleges the claims lack enablement as the term "comprising" expands the polypeptide sequence of amino acids 20-105 to include additional amino acids at the N-terminal and/or C-terminal of the polypeptide. Applicants respectfully do not agree.

The specification discloses that EG-VEGF can have a signal sequence. Full-length EG-VEGF (SEQ ID NO:2) includes a signal sequence of about 19 amino acids (see Figure 16A). The specification discloses selecting mammalian or prokaryotic signal sequences (dependent on the host cell) having a specific cleavage site at the N-terminus of mature EG-VEGF that can be used to direct secretion of EG-VEGF (page 41, lines 3-16). The specification also discloses chimeric molecules comprising EG-VEGF. For example, EG-VEGF can be fused with an epitope tag, such as a poly-his tag, to facilitate detection or purification or fused with an immunoglobulin to form a bivalent chimeric molecule (page 35, line 13 to page 36, line 11, and Example 4). Methods for making chimeric molecules are well known. Applicants therefore submit the claims are sufficiently enabled.

For the reasons discussed above, Applicants submit the specification fully enables the claims. Applicants assert the guidance and examples provided in the specification are sufficient

to enable one of skill in the art to make and use the claimed EG-VEGF polypeptides without undue experimentation. Withdrawal of the rejection is respectfully requested.

Written Description

Claims 1-12 were rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. Applicants respectfully traverse this rejection.

The Office Action acknowledges that the specification adequately describes an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2. The Office Action, however, asserts the specification does not adequately describe an isolated polypeptide comprising an amino acid sequence having at least about 80%, 85%, 90%, 95%, or 100% identity to amino acid residues 20 to 105 of SEQ ID NO:2 wherein the polypeptide promotes proliferation of ACE cells. Applicants respectfully do not agree.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. MPEP § 2163(I) (emphasis added). An Applicant may show possession of an invention by disclosure of sufficiently detailed, relevant identifying characteristics (i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between structure and function, or some combination of such characteristics) that provide evidence that Applicant was in possession of the claimed invention. *Enzo Biochem v. Gen-Probe*, 323 F.3d 956, 964 (Fed. Cir. 2002); MPEP § 2163(II)(3)(A)(a).

Applying this standard, Applicants submit the specification sufficiently describes the claimed genus of polypeptides. The amended claims are directed to a genus of polypeptides having at least 80% identity to amino acid residues 20-105 of SEQ ID NO: 2 and ACE cell proliferation activity. As discussed above, Brenner et al. discloses that sequence comparison methods are adequate and useful for predicting shared function.

As discussed above, the specification describes techniques and guidelines for making EG-VEGF variants, including amino acid sequence comparison methods and exemplary and preferred amino acid substitutions; how to isolate cDNA clones encoding EG-VEGF, including the signal sequence finding algorithm; how to use DNA comprising the coding sequence of

mature EG-VEGF, for example, as a probe to screen for homologous DNAs encoding naturally occurring variants of EG-VEGF; how to express EG-VEGF in cells; how to make antibodies that specifically bind EG-VEGF; and how to screen EG-VEGF for ACE cell proliferation activity.

In addition, angiogenic factors, such as VEGF, were known to exist in families having high amino acid sequence identity. See, for example, Table 2 below. Therefore, one of skill in the art would have reasonably expected EG-VEGF, an angiogenic factor, to be a member of a protein family (including variants and homologs) having high amino acid sequence identity. The post filing publications of LeCouter et al., Masuda et al., and Kisliouk et al. confirm that SEQ ID NO:2 is a member of a family having high amino acid sequence identity. Table 1 shows that mature mouse, rat, and bovine EG-VEGF have at least 88% amino acid sequence identity with mature human EG-VEGF (residues 20-105 of SEQ ID NO:2).

The Office Action alleges the claims lack written description as the term "comprising" expands the polypeptide sequence of amino acids 20-105 to include additional amino acids at the N- terminal and/or C-terminal of the polypeptide. Applicants respectfully do not agree.

As discussed above, the specification discloses that EG-VEGF can have a signal sequence. The specification also discloses chimeric molecules comprising EG-VEGF. For example, EG-VEGF can be fused with an epitope tag, such as a poly-his tag, to facilitate detection or purification or fused with an immunoglobulin to form a bivalent chimeric molecule (page 35, line 13 to page 36, line 11, and Example 4). Methods for making chimeric molecules are well known. Applicants therefore submit the claims satisfy the written description requirement.

In view of the forgoing, Applicants submit the specification provides sufficient written description of the claimed genus of polypeptides. Withdrawal of this rejection is respectfully requested.

Table 2

```
CLUSTAL W (1.8) multiple sequence alignment of VEGF species

Human       MNFLLSWVHWSLALLLYLHHAKWSQAAPMAEGGGQNHHEVVKFMDVYQRSYCHPIETLVD
Murine      MNFLLSWVHWTLALLLYLHHAKWSQAAPTTEGE-QKSHEVIKFMDVYQRSYCRPIETLVD
Rat         MNFLLSWVHWTLALLLYLHHAKWSQAAPTTEGE-QKAHEVVKFMDVYQRSYCRPIETLVD
Hamster     MNFLLSWVHWTLALLLYLHHAKWSQAAPTTEGE-QKAHGVVEFMDVYRRSYCHPIETLVD
Chicken     MNFLLSWVHWTLALLLYLHHAKWSQAAPTTEGE-QKAHGVVEFMDVYRRSYCHPIETLVD
Simian      MNFLLSWVHWSLALLLYLHHAKWSQAAPMAEGGGQNHHEVVKFMDVYQRSYCHPIETLVD
Porcine     MNFLLSWVHWSLALLLYLHHAKWSQAAPMAEGD-QKPHEVVKFMDVYQRSYCRPIETLVD
Bovine      MNFLLSWVHWSLALLLYLHHAKWSQAAPMAEGG-QKPHEVVKFMDVYQRSFCRPIETLVD
Sheep       MNFLLSWVHWSLALLLYLHHAKWSQAAPMAEGG-QKPHEVMKFMDVYQRSFCRPIETLVD
Canine      MNFLLSWVHWSLALLLYLHHAKWSQAAPMAGGE-HKPHEVVKFMDVYQRSYCRPIETLVD
Feline      MNFLLSWVHWSLALLLYLHHAKWSQAAPMADGE-HKPHEVVKFMDVYQRSYCRPIETLVD
Equine      MNFLLSWVHWSLALLLYLHHAKWSQAAPMAEGE-HKTHEVVKFMDVYQRSYCRPIETLVD
Frog        MNFLPSWIHWGLAVLLYIPHAQLSGAAPMPGEGDHKPTEVVKFLKVYERSMCQVREILVD
Snake       MNFLLTWIHWGLAALLYFHNAKVLQAAPAQGDGDRQQSEVIPFMTVYERSVCRPIETMVD
            **** :*:** ** ***: :*:   ***      ::   *: *: **.** *:  * :**

Human       IFQEYPDEIEYIFKPSCVPLMRCGGCCNDEGLECVPTEESNITMQIMRIKPHQGQHIGEM
Murine      IFQEYPDEIEYIFKPSCVPLMRCAGCCNDEALECVPTSESNITMQIMRIKPHQSQHIGEM
Rat         IFQEYPDEIEYIFKPSCVPLMRCAGCCNDEALECVPTSESNVTMQIMRIKPHQSQHIGEM
Hamster     IFQEYPDEIEYIFKPSCVPLMRCGGCCSDEALECVPTSESNITMQIMRVKPHQSQHIGEM
Chicken     IFQEYPDEIEYIFKPSCVPLMRCGGCCSDEALECVPTSESNITMQIMRVKPHQSQHIGEM
Simian      IFQEYPDEIEYIFKPSCVPLMRCGGCCNDEGLECVPTEESNITMQIMRIKPHQGQHIGEM
Porcine     IFQEYPDEIEYIFKPSCVPLMRCGGCCNDEGLECVPTEEFNITMQIMRIKPHQGQHIGEM
Bovine      IFQEYPDEIEFIFKPSCVPLMRCGGCCNDESLECVPTEEFNITMQIMRIKPHQSQHIGEM
Sheep       IFQEYPDEIEFIFKPSCVPLMRCGGCCNDESLECVPTEEFNITMQIMRIKPHQSQHIGEM
Canine      IFQEYPDEIEYIFKPSCVPLMRCGGCCNDEGLECVPTEEFNITMQIMRIKPHQGQHIGEM
Feline      IFQEYPDEIEYIFKPSCVPLMRCGGCCNDEGLECVPTEEFNITMQIMRIKPHQGQHIGEM
Equine      IFQEYPDEIEYIFKPSCVPLMRCGGCCNDEGLECVPTAEFNITMQIMRIKPHQSQHIGEM
Frog        IFQEYPDEVEYIFKPSCVPLMRCAGCCNDESLECVPTECYNITMQIMKIKPHISQHIMDM
Snake       IFQDYPDEVEYILKPPCVALMRCGGCCNDEALECVPTELYNVTMEIMKLKPYQSQHIHPM
            ***:****:*:*:**.**.****.***.**.******   *:**:**::**: .***  *

Human       SFLQHNKCECRPKK-DRARQENPCGPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Murine      SFLQHSRCECRPKK-DRTKPENHCEPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Rat         SFLQHSRCECRPKK-DRTKPENHCEPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Hamster     SFLQHSRCECRPKK-VRTKPENHCEPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Chicken     SFLQHSRCECRPKK-VRTKPENHCEPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Simian      SFLQHNKCECRPKK-DRARQENPCGPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Porcine     SFLQHNKCECRPKK-DRARQENPCGPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Bovine      SFLQHNKCECRPKK-DKARQENPCGPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Sheep       SFLQHNKCECRPKK-DKARQENPCGPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Canine      SFLQHSKCECRPKK-DRARQENPCGPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Feline      SFLQHSKCECRPKK-DRAK-ENPCGPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Equine      SFLQHSKCECRPKK-DKARQENPCGPCSER--RKHLFVQDPQTCKCSCKNTDSRCKARQL
Frog        SFQQHSQCECRPKKEVKSKQENHCEPCTEKSQRKHLFVQDPQTCKCSCKNTDSRCKTRQL
Snake       SFQQHSKCECRPKKETRIIQENHCEPCSER--RKHLYKQDPLTCKCSCKFTDSRCKSKQL
            ** **.:******* :   ** * **:*:  ****: *** ******* ******::**
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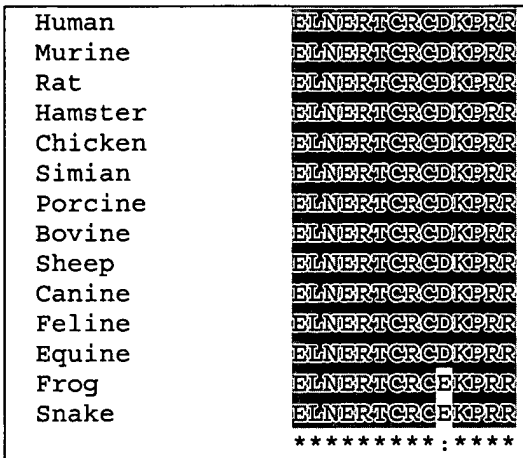

Species	Accession No.	Reference/Genbank Posting Date	% ID to human VEGF
Human	181971	Leung et al., 1989, Science, 246:1306-1309	100
Murine	40254603	Brier et al., 1992, Development, 114:521-532	89
Rat	15822721	9/03/1999	89
Hamster	17368644	Yi et al., 1999, Cell Tissue Res., 296:339-349	87
Chicken	27368068	12/23/2002	73
Simian	1839492	Shima et al., 1996, Invest. Ophthalmol. Vis. Sci., 37:1334-1340	100
Porcine	1082979	Sharma et al., 1996, Biochem. Biophys. Acta 1260:235-238	96
Bovine	27806357	U.S. 5332671; Leung et al., 1989, Science, 246:1306-1309	94
Sheep	3228693	Cheung et al., 1998, Growth Factors, 16:11-22	94
Canine	4768927	5/11/1999	95
Feline	15778148	9/25/2001	94
Equine	12082343	1/10/2001	94
Frog	2271035	7/23/1997	73
Snake	51555820	8/25/2004	71

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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Date: January 12, 2006

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